24 August 2016
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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 14-16 June 2016

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

14 June 2016, 09:00-19:00, room 2F

15 June 2016, 08:30-19:00, room 2F

16 June 2016, 08:30-15:00, room 2F

Disclaimers

Some of the information contained in this agenda is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this agenda is a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 14-16 June 2016 was adopted with amendments.

1.3. Adoption of the minutes

The minutes for 17-19 May 2016 were adopted with amendments and will be published on the EMA website.

[*Post-meeting note: The minutes from the COMP May meeting were adopted by written procedure following the COMP June plenary meeting*]

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/049/16

Prevention of hereditary angioedema attacks

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 30 May 2016, prior to responding to the list of issues.

2.1.2. Poly (oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-,amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer - EMA/OD/041/16

ERA Consulting GmbH; Treatment of hyperargininaemia

COMP coordinator: Ingeborg Barisic/Dinah Duarte

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of hyperargininemia, the sponsor is invited to elaborate on the absence of functional endpoints in the performed experiments. The sponsor should also further elaborate on the clinical relevance of the studied endpoint (arginine levels).

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action. The sponsor is invited to elaborate on the significant benefit claims versus sodium phenylbutyrate, by providing any data that support a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 14 June 2016, the sponsor developed the arguments regarding the specificity of the product on reducing hyperargininaemia in the proposed condition based on the observation that hyperammonaemia was modest and not the main driver of the detrimental effects associated with the condition. Although the condition is treated with ammonia scavengers such as sodium phenylbutyrate targeting the hyperargininaemia levels were considered of significant importance. This argument helped the COMP understand the relevance of developing an enzyme replacement therapy which would be useful in the treatment of this specific Urea Cycle Disorder. The COMP accepted that comparative or combination data with Ravicti was not needed for the assumption of significant benefit at this stage of development. The question of the relevance of the data in support of medical plausibility was also clarified.

The Committee agreed that the condition, hyperargininaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-, amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer was considered justified based on preliminary pre-clinical *in vivo* data in a model of the condition showing a reduction in hyperargininaemia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

The condition was estimated to be affecting approximately 0.06 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-, amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a reduction in hyperargininaemia

which is an important characteristic of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for poly(oxy-1,2-ethanediyl), alpha-(carboxymethyl)-omega-methoxy-, amide with arginase 1 [cobalt cofactor] (synthetic human) (1:10), trimer, for treatment of hyperargininaemia, was adopted by consensus.

2.1.3. - EMA/OD/043/16

Treatment of ovarian cancer

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 26 May 2016, prior to responding to the list of issues.

2.1.4. 3-[4-(1H-imidazol-1-ylmethyl)phenyl]-5-(2-methylpropyl)thiophene-2-[(N-butyloxylcarbamate)-sulphonamide] sodium salt - EMA/OD/046/16

Vicore Pharma AB; Treatment of idiopathic pulmonary fibrosis

COMP coordinator: Annie Lorence

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

Regarding efficacy, the sponsor is invited to provide a comparative discussion based on any available sponsor's generated and/or published data that may justify the assumption of significant benefit over the authorised medicinal products pirfenidone and nintedanib.

In addition, the COMP is of the opinion that due to the early stage of development, the claim of the sponsor of potential better safety than the currently authorized products is not acceptable.

In the written response, and during an oral explanation before the Committee on 14 June 2016, the sponsor discussed the preclinical data with the proposed product in the light of published data of the two currently authorized products, pirfenidone and nintedanib using the same preclinical model. The different measurements of fibrosis used in these studies were discussed. There is no agreed gold standard measure of lung fibrosis in preclinical studies. It was agreed that in spite of the limitations of comparing different measures of fibrosis in these three studies, overall there is enough evidence to consider that the proposed product has a comparable effect on fibrosis as the currently authorized ones in preclinical models.

The sponsor discussed the results obtained in preclinical studies where fibrosis was induced by a substance that causes pulmonary hypertension. In this model the sponsor showed that the proposed product could reduce not only lung fibrosis but also pulmonary hypertension. The mechanism of action of the proposed product supports a potential activity on pulmonary hypertension as well. In the preclinical study presented by the sponsor the proposed product, besides effects on lung fibrosis, had also shown effects on right ventricular hypertrophy (the right heart ventricle), right ventricular fibrosis and right systolic pressure -

parameters clinically relevant to an intended use in idiopathic pulmonary fibrosis (IPF) accompanied by pulmonary hypertension.

The COMP discussed the clinical relevance of pulmonary hypertension in pulmonary fibrosis. According to the sponsor up to 30% of patients with IPF, the target condition of this application, develop pulmonary hypertension (PH). Additionally, a recent report suggests that these figures could be substantially higher. PH is a very severe complication of IPF and so far there is no treatment for patients who develop PH during the course of their IPF disease. There is no treatment at the moment for PH in IPF, and development of PH is linked to high short-term mortality.

In summary, the COMP considered that the product could provide a clinically relevant advantage for the patients affected by IPF. The COMP strongly recommended protocol assistance.

The Committee agreed that the condition, idiopathic pulmonary fibrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-[4-(1H-imidazol-1-ylmethyl)phenyl]-5-(2-methylpropyl)thiophene-2-[(N-butyloxylcarbamate)-sulphonamide] sodium salt was considered justified based on preclinical data showing reduction of lung fibrosis with the proposed product in valid models of the condition.

The condition is chronically debilitating due to progressive dyspnoea and loss of lung ventilator function, heavily limiting exercise capability and decreased quality of life of the affected patients and leading in many cases within months or a few years to the need of oxygen therapy. Pulmonary hypertension usually develops. Median survival is less than five years. Death ultimately occurs due to respiratory failure.

The condition was estimated to be affecting approximately 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 3-[4-(1H-imidazol-1-ylmethyl)phenyl]-5-(2-methylpropyl)thiophene-2-[(N-butyloxylcarbamate)-sulphonamide] sodium salt will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the proposed product acts on lung fibrosis and also improves the pulmonary hypertension often associated to lung fibrosis in idiopathic pulmonary fibrosis. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for 3-[4-(1H-imidazol-1-ylmethyl)phenyl]-5-(2-methylpropyl)thiophene-2-[(N-butyloxylcarbamate)-sulphonamide] sodium salt, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.1.5. Naltrexone - EMA/OD/035/16

Able AB; Treatment of fibromyalgia

COMP coordinator: Dinah Duarte/Martin Možina

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of naltrexone for treatment of fibromyalgia (FM), the sponsor should further elaborate on:

– The mechanism of action and proof of concept regarding the use of low-dose naltrexone in the proposed condition

– The representativeness of the published studies to support the efficacy of the product in the proposed condition as it has been noted that similar products have recently shown a lack of efficacy in clinical studies in the target condition.

The sponsor is invited to present scientifically relevant data to support the potential pharmacologic activity and a plausible effect of low-dose naltrexone in patients with fibromyalgia.

- Life-threatening, seriously debilitating or serious and chronic nature of the condition

It was also noted by the COMP that in article 3(2)a second paragraph of the Orphan Regulation No(EC) 141/2000 if the applicant is seeking OD based on return of investment the condition should be life-threatening, seriously debilitating or serious and chronic. Studies show that at 2 yrs after diagnosis 47% no longer fulfil the ACR FM criteria, and remission is objectively identified in approx. 25% of the assessed patients (ref Granges G et al J Rheum 1994). This is data from adult FM. In paediatric FM similar data exist demonstrating only 51% continue to fulfil FM criteria at 6 yrs FU (ref Kashikar-Zuck S et al Paediatrics 2014). The notice on better prognosis in paediatric FM is also described by Gedalia A et al Clin Exp Rheum 2000. The sponsor should further elaborate on the life-threatening, seriously debilitating or serious and chronic nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition can be defined as life-threatening, seriously debilitating or serious and chronic.

- Insufficient return of the investment

The sponsor should further elaborate on the proposed insufficient return of the investment without incentives as the assumptions proposed only focus primarily on net present value (NPV) and do not consider the fact that this is a repurposed product as well as the impact of small to medium enterprise status on the EMA incentives which are linked to orphan designation. The COMP would also require more clarity regarding the impact of discounting and the expected pre-licencing costs and the expected return over the 10yrs of Market Exclusivity with and without the effects of the exclusivity. The sponsor should show estimated costs and sales per year before and after licensing. The sponsor should also clarify the value of the proposed prevalence as the COMP has noted that it is up to 8% of the population in the EU, in order to clarify the expected return, based on the sales for the proposed indication.

- Significant benefit

As it is accepted that there are well-established standard of care in the management of these patients the sponsor is asked to further elaborate what the significant benefit would be of using their product including nonpharmacological interventions.

In the written response, and during an oral explanation before the Committee on 15 June 2016, the sponsor discussed the life threatening and debilitating nature of the condition. According to Article 3(1)(a) of Regulation (EC) No 141/2000 if the applicant is seeking OD

based on non-return of investment, the condition should be “life-threatening, seriously debilitating or serious and chronic condition”. The sponsor acknowledged that the remission of the condition is possible (especially in “changed life situations”) and therefore the condition could not be considered chronic and serious. It was noted that patients in the milder forms learn to live with the condition and that the more severe forms generally resolve within 2 years. The COMP was of the opinion that this did not qualify the condition as serious and chronic condition. The COMP also considered that the condition was not life-threatening nor seriously debilitating.

With regards to calculation of the no return on investment, the sponsor clarified details of the assumptions of the price per tablet. This assisted the COMP to understand the basis of the lack of return on investment without incentives. The sponsor provided an estimated saving of around 7million€ regarding the overall impact of the pre-licencing incentives provided that the 10yr Market Exclusivity would be obtained. The sponsor however failed to present a counter evaluation based on the price per tablet without the incentives. The sponsor also failed to include the Cost of Goods in the estimate submitted so the real impact of the 10yr Marketing Exclusivity on profit and loss calculation as well as the net present value with and without the 10yr market Exclusivity could not be ascertained. The COMP could not therefore establish whether the sponsor had met the return on investment criteria.

The sponsor discussed the bibliographic clinical data submitted and the COMP requested further clarification regarding the medical plausibility. The sponsor did not submit any new clinical data for discussion compared to the initial submission. The two publications used were considered to be too short and used the wrong clinical design to establish the relevance of using the product in the condition. Of particular concern was the cross-over design and short term treatment period. The short term data provided by the sponsor did not seem to adequately support the medical plausibility.

The same clinical bibliographic data did not clearly establish how patients were currently managed and what would be the significant benefit of using the proposed product if any of the non-pharmacological treatment methods were considered to offer a valid treatment option.

As the use of the sponsor’s product in the condition was not clearly explained in the two publications provided nor during the oral explanation, the COMP was therefore of the opinion that insufficient data had been submitted to support a significant benefit of the product in the condition, if applicable.

A negative opinion for naltrexone, for treatment of fibromyalgia, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.1.6. Adeno-associated viral vector serotype 2.7m8 containing the chrimsonR-tdTomato gene - EMA/OD/028/16

GenSight Biologics; Treatment of retinitis pigmentosa

COMP coordinator: Ingeborg Barisic/Armando Magrelli

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of retinitis pigmentosa, the sponsor should further elaborate on:

- The preclinical study, focussing on experimental methodology, level of evidence and outcomes.
- The availability of functional outcome data in relevant disease models demonstrating an improvement in vision.

In the written response, and during an oral explanation before the Committee on 14 June 2016, the sponsor has provided the necessary study reports to ascertain that a sufficient amount of evidence has been generated in the preclinical experiments. The sponsor also clarified that further preclinical data on optomotor testing in this model will be collected in due time.

The COMP considered that for the purpose of orphan designation only part of the data submitted was considered relevant. The results demonstrated that treatment was able to restore photosensitivity in photo-insensitive retinas from a valid disease model.

The Committee agreed that the condition, retinitis pigmentosa, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 2.7m8 containing the *ChrimsonR-tdTomato* gene was considered justified based on preclinical data demonstrating that treatment was able to restore photosensitivity of the retina in a valid disease model.

The condition is chronically debilitating due the development of nyctalopia and tunnel vision progressing to total blindness.

The condition was estimated to be affecting less than 3.7 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for adeno-associated viral vector serotype 2.7m8 containing the *ChrimsonR-tdTomato* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.1.7. - EMA/OD/042/16

Treatment of Clostridium difficile infection

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor has submitted an incidence calculation based on several publications which would support a value below 5 in 10,000. The COMP has noted that the diagnosis and reporting of the condition has been increasing in recent years. It was also noted that there is a recent publication from the European Centre for Disease Prevention and Control, 2015 which highlights that a “point-prevalence survey of healthcare associated infections and antimicrobial use in European hospitals between 2011-2012 indicated that *Clostridium*

difficile infections were responsible for 48% of all gastro-intestinal health care associated infections, and for 3.6% of all healthcare-associated infections". This report also highlights an increase in the incidence of *Clostridium difficile* infection in Europe and the existance of registries.

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, and during an oral explanation before the Committee on 15 June 2016, the sponsor presented a revised incidence calculation for *Clostridium difficile* infection. A presentation based primarily on hospital reporting of the condition was the primary basis of the calculation with assumption presented regarding a low nosocomial rate in the out-of-hospital setting. The COMP considered that assumptions made regarding the inclusion of nosocomial reporting were inadequately represented for Europe thereby representing an underestimate of the incidence of the condition in Europe and that the incidence was higher than what was being presented.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 June 2016, prior to final opinion.

2.1.8. - EMA/OD/048/16

Treatment of sporadic lymphangioleiomyomatosis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

As per sponsor application, Lymphangioleiomyomatosis (LAM) is a pulmonary disease of women of reproductive age characterized by progressive cystic lung destruction, and extra-pulmonary abnormalities consisting of abdominal tumors (e.g. angiomyolipomas), lymphatic tumors (e.g. lymphangioleiomyomas), and chylous effusions. In this context, the sponsor is invited to discuss if angiomyolipoma is considered to be a distinct medical entity or can be considered to be a part of the medical entity lymphangioleiomyomatosis. The sponsor is asked to elaborate on pathophysiology, histopathology, clinical characteristics and classifications.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of lymphangioleiomyomatosis, the sponsor should further elaborate on:

- The availability of valid preclinical *in vivo* models for the condition.
- The relevance of the preclinical model to predict clinical efficacy and the availability of additional data with the proposed product in valid *in vivo* models or patients affected by the condition.

- Number of people affected

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor should describe and justify the methodology used for the prevalence calculation. Specifically, the sponsor is invited to discuss if TSC-LAM patients might have already been captured by the worldwide LAM registry data leading to an overestimation of prevalence by combining the prevalence of TSC-LAM and LAM patients.

- Significant benefit

No significant benefit argumentation has been submitted. Everolimus (Votubia) is authorised for renal angiomyolipoma associated with tuberous sclerosis complex (TSC). As per above discussion on the condition definition, the sponsor should be prepared to provide a data-driven significant benefit argumentation versus everolimus (Votubia).

In the written response, and during an oral explanation before the Committee on 15 June 2016, the sponsor outlined that angiomyolipoma is to be considered as a co-morbidity of LAM. The sponsor proposes lymphangioleiomyomatosis (LAM) to be a distinct medical entity that can be separated into two subforms: the inherited LAM that is associated with tuberous sclerosis complex (TSC-LAM) and the sporadic LAM. The COMP recognised that there is an intersection between TSC-LAM and tuberous sclerosis complex (TSC), which the COMP has previously designated as a distinct medical entity for the purpose of orphan designation. For that reason, the COMP decided to adequately differentiate the LAM sub-entities by designating the orphan condition "sporadic lymphangioleiomyomatosis". This approach avoids any intersection in patient populations and establishes two distinct orphan conditions: sporadic LAM and TSC. TSC-LAM patients are considered by the COMP to fall under the orphan condition of "tuberous sclerosis complex". This further clarifies that no products are authorised in sporadic LAM and no significant benefit has to be established for this orphan designation application.

Regarding the medical plausibility, the sponsor acknowledged that no additional data are available at this point in time. The sponsor is however in contact with experts in the field planning to test the product in a valid preclinical model. While the COMP acknowledged the preliminary in vitro data that is available, it also decided that the data was not sufficient to establish medical plausibility for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 June 2016, prior to final opinion.

2.1.9. Sirolimus - EMA/OD/045/16

Best Regulatory Consulting Ltd; Treatment of sporadic lymphangioleiomyomatosis

COMP coordinator: Bożenna Dembowska-Bagińska

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

As per sponsor application, lymphangioleiomyomatosis (LAM) is a pulmonary disease of women of reproductive age characterized by progressive cystic lung destruction, and extra-pulmonary abnormalities consisting of abdominal tumors (e.g. angiomyolipomas), lymphatic

tumors (e.g. lymphangioleiomyomas), and chylous effusions. In this context, the sponsor is invited to discuss if angiomyolipoma is considered to be a distinct medical entity or can be considered to be a part of the medical entity lymphangioleiomyomatosis. Please elaborate on pathophysiology, histopathology, clinical characteristics and classifications.

- Significant benefit

No significant benefit argumentation has been submitted. Everolimus (Votubia) is authorised for renal angiomyolipoma associated with tuberous sclerosis complex (TSC). As per above discussion on the condition definition, the sponsor should be prepared to provide a data-driven significant benefit argumentation versus everolimus (Votubia).

In the written response, and during an oral explanation before the Committee on 15 June 2016, the sponsor outlined that angiomyolipoma - in general and/or associated with tuberous sclerosis complex - is to be considered as a distinct medical entity. The sponsor proposes lymphangioleiomyomatosis (LAM) to be a distinct medical entity that can be separated into two subforms: the inherited LAM that is associated with tuberous sclerosis complex (TSC-LAM) and the sporadic LAM.

The COMP recognised that there is an intersection between TSC-LAM and tuberous sclerosis complex (TSC), which the COMP has previously designated to be a as a distinct medical entity for the purpose of orphan designation. For that reason, the COMP decided to adequately differentiate the LAM sub-entities by designating the orphan condition “sporadic lymphangioleiomyomatosis”. This approach avoids any intersection in patient populations and establishes two distinct orphan conditions: sporadic LAM and TSC. TSC-LAM patients are considered by the COMP to fall under the orphan condition of “tuberous sclerosis complex”. This further clarifies that no products are authorised in sporadic LAM and no significant benefit has to be established for this orphan designation application.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of sporadic lymphangioleiomyomatosis.

The Committee agreed that the condition, sporadic lymphangioleiomyomatosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on preliminary clinical data demonstrating a stabilisation of lung function in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to the progressive decline of lung function resulting in respiratory failure, recurrent pneumothoraces, chylous pleural effusions, haemorrhages and abdominal or pelvic tumour masses.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for sirolimus, for treatment of sporadic lymphangioleiomyomatosis, was adopted by consensus.

2.1.10. Dimethyl fumarate - EMA/OD/029/16

Immungenetics AG; Treatment of bullous pemphigoid

COMP coordinator: Josep Torrent-Farnell

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor provides a discussion of incidence data from publications and derives prevalence estimate assuming a median duration of the disease of 10 years. In publications mentioned by the sponsor, comments of increasing incidence in the EU are made and higher incidence values are mentioned.

The sponsor is invited to discuss the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

In the written response, the sponsor included information on the most recent publication from Germany (Huebner et al 2016), which estimates the prevalence based on the database of a large German health insurance company. The sponsor acknowledged the fact that there are sources indicating an increase in prevalence of bullous pemphigoid. This change is attributed to the increase in the incidence of autoimmune conditions as well as the aging of the European population. The sponsor proposed the most conservative approach for the estimate of prevalence amounting to 2.59 in 10,000 persons in the EU. The committee considered this response and estimated it satisfactory at this stage. A more thorough research of prevalence might be expected to confirm this estimate at the time of marketing authorisation.

The Committee agreed that the condition, bullous pemphigoid, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing dimethyl fumarate was considered justified based on preliminary clinical data demonstrating induction of remission in patients treated with the product in combination with topical glucocorticoid.

The condition is life-threatening due to treatment induced immunosupression and chronically debilitating due to tense blisters, erythema, urticarial plaques, skin erosions and crusts, severe pruritus and oral lesions.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing dimethyl fumarate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product has a potential to induce remission in patients who are not responding to systemic corticosteroid treatment or who are advised not to receive such treatment. In addition, the efficacy of the product was achieved in combination with topical glucocorticoid ointment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for dimethyl fumarate, for treatment of bullous pemphigoid, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. 16-base single-stranded peptide nucleic acid oligonucleotide linked to a 7 aminoacid peptide - EMA/OD/037/16

Biogenera SpA; Treatment of soft tissue sarcoma

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 16-base single-stranded peptide nucleic acid oligonucleotide linked to a 7 aminoacid peptide was considered justified based on pre-clinical data showing a reduction in tumour size which is dose dependant.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 16-base single-stranded peptide nucleic acid oligonucleotide linked to a 7 aminoacid peptide (Chemical) will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical *in vivo* data that demonstrate tumour reduction targeting the N-Myc positive cells with an alternative mode of action in rhabdomyosarcoma which is dose dependant. The committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 16-base single-stranded peptide nucleic acid oligonucleotide linked to a 7 aminoacid peptide, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.2. 2-[4-(1-Methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline succinic acid - EMA/OD/066/16

Pfizer Limited; Treatment of Huntington's disease

COMP coordinator: Violeta Stoyanova

The Committee agreed that the condition, Huntington's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline succinic acid was considered justified based on preclinical data demonstrating treatment effects on neuronal signal transduction, supported by preliminary clinical data demonstrating that treatment improved grip strength in the context of goal-directed behaviour.

The condition is life-threatening and chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline succinic acid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the treatment can improve goal-directed behaviour or motivation in patients affected by the condition. These aspects of the condition are currently not sufficiently managed by the current standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline succinic acid, for treatment of Huntington's disease, was adopted by consensus.

2.2.3. - EMA/OD/079/16

Treatment of narcolepsy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.4. - EMA/OD/050/16

Treatment of Huntington’s disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.5. - EMA/OD/080/16

Treatment of graft versus host disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.6. - EMA/OD/078/16

Treatment of idiopathic dilated cardiomyopathy

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.7. Autologous CD4 and CD8 T cells transduced with lentiviral vector containing an affinity-enhanced T cell receptorto target the cancer-testis tumor antigen NY-ESO-1 - EMA/OD/064/16

Adaptimmune Limited; Treatment of soft tissue sarcoma

COMP coordinator: Katerina Kopečková

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to autologous CD4+ and CD8+ T-cells transduced with lentiviral vector

containing an affinity-enhanced T-cell receptor targeting the New York esophageal antigen-1.

The Committee agreed that the condition, soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD4+ and CD8+ T-cells transduced with lentiviral vector containing an affinity-enhanced T-cell receptor targeting the New York esophageal antigen-1 was considered justified based on preliminary clinical data demonstrating that patients responded to treatment.

The condition is life-threatening and chronically debilitating due the high recurrence and metastasis rate leading to an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD4+ and CD8+ T-cells transduced with lentiviral vector containing an affinity-enhanced T-cell receptor targeting the New York esophageal antigen-1 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that patients responded to treatment. The overall response rate compared favourably to published literature data for authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD4+ and CD8+ T-cells transduced with lentiviral vector containing an affinity-enhanced T-cell receptor targeting the New York esophageal antigen-1, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.8. Autologous Epstein-Barr Virus specific T-cells derived from peripheral blood mononuclear cells, expanded ex vivo - EMA/OD/075/16

Cell Medica Ltd.; Treatment of extranodal NK/T cell lymphoma, nasal type

COMP coordinator: Frauke Naumann-Winter

The Committee agreed that the condition, extranodal NK/T-cell lymphoma, nasal type, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous Epstein-Barr virus specific T cells derived from peripheral blood mononuclear cells, expanded ex vivo was considered justified based on preliminary clinical data in patients with active disease who showed a complete or partial remission.

The condition is life-threatening due to an average survival rate between 6 and 25 months from diagnosis and chronically debilitating due to aggressive, locally destructive midfacial necrotizing lesions.

The condition was estimated to be affecting approximately 0.08 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the

assumption that the medicinal product containing autologous Epstein-Barr virus specific T cells derived from peripheral blood mononuclear cells, expanded ex vivo will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a complete response in some patients who have relapsed extranodal NK/T cell lymphoma, nasal type. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous Epstein-Barr virus specific T cells derived from peripheral blood mononuclear cells, expanded ex vivo, for treatment of extranodal NK/T-cell lymphoma, nasal type, was adopted by consensus.

2.2.9. Autologous Epstein-Barr Virus specific T-cells derived from peripheral blood mononuclear cells, expanded ex vivo - EMA/OD/076/16

Cell Medica Ltd.; Treatment of post-transplantation lymphoproliferative disorders

COMP coordinator: Bożenna Dembowska-Bagińska

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of post-transplant lymphoproliferative disorder.

The Committee agreed that the condition, post-transplant lymphoproliferative disorder, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous Epstein-Barr virus specific T cells derived from peripheral blood mononuclear cells, expanded ex vivo was considered justified based on preliminary clinical data showing complete response in patients who were refractory.

The condition is life-threatening due to fulminant and lethal course of the disease and chronically debilitating due to transplant specific organ dysfunction, malaise, lethargy, weight loss and fever.

The condition was estimated to be affecting approximately 1.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous Epstein-Barr virus specific T cells derived from peripheral blood mononuclear cells, expanded ex vivo will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete response in patients who are refractory to previous treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous Epstein-Barr virus specific T cells derived from peripheral blood mononuclear cells, expanded ex vivo, for treatment of post-transplant lymphoproliferative disorder, was adopted by consensus.

2.2.10. - EMA/OD/069/16

Treatment of tracheal stenosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.11. Brincidofovir - EMA/OD/070/16

Chimerix UK Ltd; Treatment of adenovirus infection

COMP coordinator: Bożenna Dembowska-Bagińska

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of adenovirus infection in immunocompromised patients.

The Committee agreed that the condition, adenovirus infection in immunocompromised patients, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing brincidofovir was considered justified based on clinical data showing significant reduction or clearance of viremia in patients treated with the proposed product.

The condition is life-threatening due to frequent development of acute severe hepatitis, pneumonitis, colitis, haemorrhagic cystitis, and encephalitis. Disseminated disease can be rapidly fatal, with mortality rates reported to be as high as 80%.

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for brincidofovir, for treatment of adenovirus infection in immunocompromised patients, was adopted by consensus.

2.2.12. - EMA/OD/081/16

Treatment of amyotrophic lateral sclerosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.13. - EMA/OD/051/16

Treatment of West Nile virus infection

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.14. Mifamurtide - EMA/OD/071/16

Delta Proteomics SAS; Treatment of echinococcosis

COMP coordinator: Nikolaos Sypsas

The Committee agreed that the condition, echinococcosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mifamurtide was considered justified based on preclinical *in vivo* data demonstrating cyst growth inhibition when used in combination with albendazole.

The condition is life-threatening due to anaphylactic shock in the event of cyst rupture and chronically debilitating due to pain, tumour-like cyst growth, biliary duct obstruction, nausea

and vomiting, chronic cough, chest pain, shortness of breath, fever, urticaria and eosinophilia.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mifamurtide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the combination of the product with albendazole has a synergistic effect, leading to a significant inhibition of cysts growth. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mifamurtide, for treatment of echinococcosis, was adopted by consensus.

2.2.15. Mifamurtide - EMA/OD/072/16

Delta Proteomics SAS; Treatment of hepatocellular carcinoma

COMP coordinator: Bożenna Dembowska-Bagińska

The Committee agreed that the condition, hepatocellular carcinoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mifamurtide was considered justified based on preclinical *in vivo* data demonstrating reduction in the tumour growth following partial hepatectomy.

The condition is life-threatening and chronically debilitating due to increased mortality and liver dysfunction. Median survival without therapy can be greater than 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

The condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mifamurtide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the portal administration of the product significantly reduces the number of tumour nodules in a model of the minimal residue disease following tumour resection compared to controls. Tumour resection is recommended in patients with early stages of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mifamurtide, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2.16. Recombinant human monoclonal antibody to insulin receptor - EMA/OD/040/16

XOMA UK Limited; Treatment of congenital hyperinsulinism

COMP coordinator: Vallo Tillmann

The Committee agreed that the condition, congenital hyperinsulinism, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human monoclonal antibody to insulin receptor was considered justified based on preclinical *in vivo* data demonstrating normalisation of fasting glucose levels in models of hyperinsulinism.

The condition is life-threatening due to severe hypoglycaemia and chronically debilitating due to symptoms of hypoglycaemia such as pallor, sweat, tachycardia and neurological effects of chronic hypoglycaemia.

The condition was estimated to be affecting less than 0.15 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for recombinant human monoclonal antibody to insulin receptor, for treatment of congenital hyperinsulinism, was adopted by consensus.

2.2.17. - EMA/OD/077/16

Treatment of paroxysmal nocturnal haemoglobinuria

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.18. Setmelanotide - EMA/OD/063/16

TMC Pharma Services Ltd; Treatment of pro-opiomelanocortin deficiency

COMP coordinator: Violeta Stoyanova/Dinah Duarte

The Committee agreed that the condition, pro-opiomelanocortin deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing setmelanotide was considered justified based on clinical data demonstrating reduction of hunger score and significant weight loss in patients.

The condition is life-threatening due to failure to thrive in infancy and secondary adrenal insufficiency and chronically debilitating due to morbid obesity and endocrinopathies.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for setmelanotide, for treatment of pro-opiomelanocortin deficiency, was adopted by consensus.

2.2.19. - EMA/OD/054/16

Treatment of N-acetylglutamate synthase deficiency

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.20. - EMA/OD/055/16

Treatment of lysinuric protein intolerance

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.21. - EMA/OD/056/16

Treatment of ornithine translocase deficiency

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.22. Sodium benzoate - EMA/OD/057/16

Lucane Pharma SA; Treatment of carbamoylphosphate synthetase I deficiency

COMP coordinator: Annie Lorence

The Committee agreed that the condition, carbamoylphosphate synthetase I deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that the product could normalise serum ammonia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of carbamoylphosphate synthetase I deficiency, was adopted by consensus.

2.2.23. Sodium benzoate - EMA/OD/058/16

Lucane Pharma SA; Treatment of citrullinaemia type 1

COMP coordinator: Annie Lorence

The Committee agreed that the condition, citrullinaemia type 1, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that the product could normalise serum ammonia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of citrullinaemia type 1, was adopted by consensus.

2.2.24. - EMA/OD/059/16

Treatment of argininosuccinic aciduria

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.25. Sodium benzoate - EMA/OD/060/16

Lucane Pharma SA; Treatment of argininaemia

COMP coordinator: Annie Lorence

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of hyperargininaemia.

The Committee agreed that the condition, hyperargininaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on one published case report demonstrating that the product could normalise serum ammonia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be

used in combination with the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of hyperargininaemia, was adopted by consensus.

2.2.26. Sodium benzoate - EMA/OD/053/16

Lucane Pharma SA; Treatment of ornithine transcarbamylase deficiency

COMP coordinator: Annie Lorence

The Committee agreed that the condition, ornithine transcarbamylase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on published case reports demonstrating that the product could normalise serum ammonia.

The condition is life-threatening and chronically debilitating due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate will be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium benzoate, for treatment of ornithine transcarbamylase deficiency, was adopted by consensus.

2.2.27. Sodium hypochlorite - EMA/OD/068/16

Hypo-Stream Ltd; Treatment of partial deep dermal and full thickness burns

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, partial deep dermal and full thickness burns, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium hypochlorite was considered justified based on preliminary clinical data showing improved survival.

The condition is chronically debilitating due to the formation of extensive scarring that causes disfigurement, pain, itching, impairment of mobility and need for surgery. The condition is also life-threatening due to multi-organ failure and sepsis.

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium hypochlorite will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improved survival in patients with large total body surface area burns. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium hypochlorite, for treatment of partial deep dermal and full thickness burns, was adopted by consensus.

2.2.28. Triheptanoin - EMA/OD/074/16

Vall d'Hebron Institute of Research; Treatment of McArdle disease

COMP coordinator: Michel Hoffmann

The Committee agreed that the condition, McArdle's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing triheptanoin was considered justified based on preliminary clinical data showing an improvement in skeletal muscle function.

The condition is life-threatening due to acute rhabdomyolysis and chronically debilitating due to exercise intolerance consisting of acute crises of early fatigue and muscle stiffness and contractures. This is sometimes accompanied by rhabdomyolysis and myoglobinuria. Acute rhabdomyolysis carries a mortality of 8%.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for triheptanoin, for treatment of McArdle's disease, was adopted by consensus.

2.2.29. - EMA/OD/073/16

Treatment of McArdle disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July meeting.

2.2.30. Volanesorsen sodium - EMA/OD/082/16

Ionis USA Ltd; Treatment of familial partial lipodystrophy

COMP coordinator: Josep Torrent-Farnell

The Committee agreed that the condition, familial partial lipodystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing volanesorsen sodium was considered justified based on preclinical data showing reduction of lipid serum levels in valid preclinical models of the condition.

The condition is life-threatening and chronically debilitating due to metabolic complications such as diabetes, hypertriglyceridemia, low HDL cholesterol levels causing increased mortality from cardiovascular disease; in addition patients affected by the condition are at higher risk of acute pancreatitis, a severe complications characterized by elevated mortality.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for volanesorsen sodium, for treatment of familial partial lipodystrophy, was adopted by consensus.

2.2.31. - EMA/OD/067/16

Treatment of glioma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee at the July meeting.

2.3. Revision of the COMP opinions

None

2.4. COMP opinions adopted via written procedure following previous meeting

None

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP coordinators

COMP coordinators were appointed for 40 applications submitted.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 32 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of microscopic polyangiitis

The discussion was postponed.

3.1.2. -

Treatment of granulomatosis with polyangiitis

The discussion was postponed.

3.1.3. -

Treatment of acute myeloid leukaemia

The Committee was briefed on the significant benefit issues. The proposed answers on significant benefit issues will be circulated for adoption via written procedure.

[Post-meeting note: The COMP adopted the proposed answers by written procedure following its June plenary meeting.]

3.1.4. -

Treatment of growth hormone deficiency

The Committee was briefed on the significant benefit issues. The COMP proposed answers on significant benefit issues will be circulated for adoption via written procedure.

[Post-meeting note: The COMP adopted the proposed answers by written procedure following its June plenary meeting.]

3.2. Finalised letters

3.2.1. -

Treatment of primary sclerosing cholangitis

The finalised letter was circulated for information.

3.2.2. -

Treatment of beta thalassaemia intermedia and major

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of soft tissue sarcoma

The new request was noted.

4. Review of orphan designation for orphan medicinal products for marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

4.1.1. Revlimid – lenalidomide - Type II variation - EMA/OD/078/11, EU/3/11/924, EMEA/H/C/000717/II/0079

Celgene Europe Limited; Treatment of mantle cell lymphoma

COMP coordinator: Jens Ersbøll and Daniel O'Connor; CHMP rapporteur: Pierre Demolis; CHMP co-rapporteur: Filip Josephson

In its written grounds of appeal, and during an oral explanation before the Committee on 15 June 2016, the sponsor submitted a re-analysis of study MCL-002, the pivotal study on which the MA was based (randomised controlled trial vs investigator's best choice, PFS, n=254), and a more-in depth analysis of the ongoing study MCL-004 (observational, uncontrolled), of which data have been presented with the cut-off date 18 April 2016. The latter study was started by the sponsor in agreement with a protocol assistance procedure requested following the MA submission of ibrutinib (Imbruvica) in order to explore how to demonstrate the significant benefit of Revlimid vs. Imbruvica.

In the re-analysis of study MCL-002 the sponsor identified a sub-population of patients that would have not been eligible to treatment with ibrutinib based on its SmPC. Ibrutinib is not recommended for patients with risk of bleeding or atrial fibrillation requiring anticoagulants. This population is well described in the ibrutinib SmPC and according to a literature search performed by the sponsor it would amount to up to 13% of all population eligible for a study such as MCL-002 (patients with relapsed or refractory mantle cell lymphoma). The population not eligible for ibrutinib was extrapolated from the MCL-002 trial based on the pre-existing characteristics at the start of the study. This yielded a subset of 70 patients, differently distributed between the trial arms (60 in the lenalidomide arm, 18 in the placebo arm). The sponsor presented the results of lenalidomide-treated patients showing an ORR of 48.3%, in line with the effect of the whole lenalidomide arm (ORR 45.9%).

The sponsor also compared indirectly in the discussion the DoR from this study (17.1 months) with the one in an open-label ibrutinib study on 111 patients (17.5), concluding that lenalidomide would be a valid therapeutic alternative in this patient population.

The second argument for the significant benefit was based on the additional discussion presented by the sponsor on study MCL-004 at the 18 April cut-off. The conclusions that can be drawn are limited not only by the nature but also by the small size of the study that so far consists of 48 patients. The sponsor analysed separately the patients that got lenalidomide as monotherapy and those where lenalidomide was administered as

combination therapy. It was noted by the sponsor and confirmed by the COMP that while the numbers are small for a clear conclusion on monotherapy (n=10 patients), 2 patients did respond, resulting in an ORR of 20%. In addition, treatment with lenalidomide allowed for one patient to discontinue after 12.5 weeks in order to undergo stem-cell transplantation with curative intent following the lenalidomide-induced response. The patient received the transplant and remains alive.

In conclusion the company has followed protocol assistance and made two plausible arguments in the view of the COMP and EMA coordinators that in those patients who either should not be treated with ibrutinib or those patients who have failed ibrutinib, lenalidomide could have meaningful clinical outcomes in line with a definition of clinically relevant advantage.

The COMP concluded that:

The proposed therapeutic indication, treatment of adult patients with relapsed or refractory mantle cell lymphoma falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of mantle cell lymphoma.

The prevalence of mantle cell lymphoma (hereinafter referred to as “the condition”) is estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, fever, and weight loss. Median survival is 3 to 5 years.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the significant benefit of lenalidomide to those affected by the orphan condition has been confirmed. This is considered justified based on the analysis of the main pivotal trial in patients with mantle cell lymphoma who were refractory to their regimen or had relapsed once or more times. In this study, where lenalidomide was used as monotherapy, the sponsor identified a patient population that was not eligible for treatment with ibrutinib, currently indicated for the same therapeutic use as lenalidomide in this stage of disease. The population identified by the sponsor as not eligible for treatment with ibrutinib represented a relevant part of the study population. In this group the sponsor showed that lenalidomide resulted in favourable response rates with the same effect size as the whole lenalidomide treated group. The COMP considered that the possibility of effectively treating patients with lenalidomide that are not eligible for ibrutinib represents a clinically relevant advantage for the patients affected by mantle cell lymphoma, in line with recently published treatment recommendations.

An opinion not recommending the removal of Revlimid, lenalidomide (EU/3/11/924) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP opinion was formally adopted by written procedure following the June plenary meeting.]

4.1.2. NINLARO - ixazomib – EMEA/H/C/003844, EU/3/11/899, EMA/OD/048/11

Takeda Pharma A/S; Treatment of multiple myeloma

CHMP rapporteur: Greg Markey; CHMP co-rapporteur: Daniela Melchiorri

CHMP negative opinion was noted.

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

4.2.1. Zalmoxis - allogeneic T cells genetically modified to express suicide gene - EMEA/OD/041/03, EU/3/03/168, EMEA/H/C/002801

MolMed SpA; Adjunctive treatment in haematopoietic cell transplantation

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to elaborate on the following issues:

The sponsor is invited to provide a full discussion and methodology on how the updated prevalence has been calculated. In addition please be clear if data from all EU member states have been included, and if data from all underlying conditions and not only AML have been included.

The sponsor is requested to provide a complete list of all currently authorised products in the therapeutic condition. This should include products mentioning haematopoietic stem cell transplantation in 4.1 of the SmPC and products used in mentioning haematopoietic stem cell transplantation patients that might be indicated in broader terms, including products for the treatment of infections or immunodeficiency in immunocompromised patients and products for the management of graft versus host disease.

The sponsor is requested to provide a significant benefit argumentation by putting the clinical outcome data into context of the best standard of care including all authorised products. In this context, the sponsor should outline the specific treatments of the study population and of the historic control patients received in addition to the product.

In its written response, and during an oral explanation before the Committee on 16 June 2016, the sponsor has submitted an updated prevalence calculation that takes into consideration the incidence of haematopoietic stem cell transplantation as reported in the annual activity survey of the European Society of Blood and Marrow Transplantation (EBMT) in all EU-28 states except Malta. The presented report stems from 2014, and by taking into account a 4% annual increase the sponsor estimates a prevalence rate in 2016 of 0.32 per 10,000. The COMP considered this updated calculation sufficient to demonstrate that the prevalence of the orphan condition remains below 5 in 10,000.

Regarding the existing methods, the sponsor has provided an extensive list of medicinal products in use as adjunct to haematopoietic stem cell transplantation including anti-infectious agents, growth factors, immunosuppressive medicines, serum-prophylaxis agents, vaccines, and one CXCR4 antagonist. The COMP acknowledged this list as sufficient as a basis to discuss significant benefit.

Regarding significant benefit, the sponsor has presented the results of its clinical data with Zalmoxis treatment in patients with T-cell depleted haploidentical transplant in comparison to contemporaneous cases transplanted with haploidentical HSCT and reported to the EBMT Registry (the control group). For the Zalmoxis group, data were pooled from patients receiving Zalmoxis after haploidentical T-cell depleted HSCT in the phase I/II trial TK007 (n=30) and in the experimental arm of the ongoing phase III trial TK008 (n=15). For the

control group, data were collected from patients undergoing haploidentical transplants performed according to the two mostly used modalities of GvHD prevention: T-cell depleted transplant without any add-back strategy and T-cell deplete (unmanipulated) transplant followed by post-graft infusion of cyclophosphamide and immune suppression with a calcineurin inhibitor and mycophenolate mofetil. The pair-matched analysis showed an increase of 17% in one-year overall survival rate for the Zalmoxis group compared with the control group (51% vs 34%, respectively; p=0.007), a decrease of 26% in the one-year non-relapse mortality for the Zalmoxis group compared with the control group (20% vs 46%, respectively; p=0.003), and a reduction in incidence of chronic GvHD (6% vs 25%, respectively; p=0.02).

The COMP acknowledged the positive outcome of this analysis and discussed with the sponsor the use of authorised products in the historic control group and in the Zalmoxis studies to understand the significant benefit of Zalmoxis in the context of the current standard of care. With regards to the patients in the Zalmoxis studies, the sponsor confirmed that the enrolled patients did not receive any further concomitant medication to Zalmoxis apart from the suicide inducer ganciclovir. With regards to the control group of the pair-matched analysis, the sponsor outlined that no information on the specific treatments administered were captured by the EBMT Registry. The sponsor however confirmed that the control patients received the best standard of care for controlling the main complications and causes of death after allogeneic or haploidentical transplant: infection and chronic GvHD. In conclusion, even though specific details on the use of authorised products were not available, the COMP considered that the presented clinical results demonstrate a significant benefit of Zalmoxis in the context of the current best standard of care on the grounds of a clinically relevant advantage.

The COMP concluded that:

The proposed therapeutic indication, adjunctive treatment in haploidentical haematopoietic stem-cell transplantation of adult patients with high-risk haematological malignancies falls entirely within the scope of the orphan indication of the designated orphan medicinal product Adjunctive treatment in haematopoietic cell transplantation.

The prevalence of Adjunctive treatment in haematopoietic cell transplantation (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 0.32 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease>

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Zalmoxis may be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The treatment with Zalmoxis improved overall survival, reduced non-relapse mortality, and reduced the incidence of chronic graft versus host disease in patients undergoing haploidentical haematopoietic stem cell transplantation. This compared favourably to historic registry data from patients receiving best standard of care.

An opinion not recommending the removal of Zalmoxis, herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes, allogeneic T cells genetically modified with a retroviral vector encoding for a

truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) (EU/3/03/168) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[Post-meeting note: The COMP opinion was formally adopted by written procedure following the June plenary meeting.]

4.2.2. Kyndrisa - drisapersen – EMA/OD/121/12, EU/3/12/1077, EMEA/H/C/003846

BioMarin International Limited; Treatment of Duchenne muscular dystrophy

The discussion was cancelled as the Marketing Authorisation Application had been withdrawn after the CHMP May meeting.

4.2.3. Arikayce - amikacin –EMA/OD/024/06, EU/3/06/387, EMEA/H/C/003936

Insmed Limited;

a) Treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis (EMA/OD/024/06, EU/3/06/387)

b) Treatment of nontuberculous mycobacterial lung disease (EMA/OD/191/13, EU/3/14/1259)

The discussion was cancelled as the Marketing Authorisation Application had been withdrawn after the CHMP May meeting.

4.2.4. - parathyroid hormone – EMA/OD/102/13, EU/3/13/1210, EMEA/H/C/003861

NPS Pharma Holdings Limited; Treatment of hypoparathyroidism

The status of the procedure at CHMP was noted.

4.2.5. - mercaptamine – EMA/OD/036/08, EU/3/08/578, EMEA/H/C/003769

Orphan Europe S.A.R.L.; Treatment of cystinosis

The status of the procedure at CHMP was noted.

4.2.6. - chenodeoxycholic acid – EMA/OD/196/14, EU/3/14/1406, EMEA/H/C/004061

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee in the coming months (depending on outcome of discussions at CHMP).

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 3 applications.

4.4. Public Summary of Opinion

The draft public summary of the COMP opinion adopted last month was endorsed for publication on the EMA website.

5. Application of Article 8(2) of the Orphan Regulation

None

6. Organisational, regulatory and methodological matters

6.1. Mandate and organisation of the COMP

6.1.1. Strategic Review & Learning meetings

Report from the Strategic Review & Learning meeting in Utrecht (NL), 31 May-1 June 2016

COMP members who could not attend the meeting organised by the Presidency of the Council of European Union in Utrecht were informed of the discussions and outcomes of the meeting. The final agenda and presentations were made available in MMD.

EMA asked for volunteers to start with the preparation of the COMP internal workshop on conditions to be held in December.

[*Post-meeting note: The minutes from the meeting in Utrecht will be tabled for information at the July COMP plenary meeting*]

6.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 14 June 2016.

6.1.3. COMP Drafting Group

The COMP Drafting group met on 15 June 2016.

6.1.4. Organisation of COMP November meeting 2016

EMA reminded COMP that due to an EMA bank holiday, the November COMP plenary meeting will be held over two days. Depending on the workload, a virtual meeting may be organised during the week preceding the plenary to start discussions.

6.2. Coordination with EMA Scientific Committees or CMDh-v

6.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place on 15 June 2016 by teleconference.

6.2.2. Recommendations on eligibility to PRIME – report from CHMP

The Chair presented PRIME eligibility process and the outcome of the CHMP first discussions on eligibility.

6.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

None

6.4. Cooperation within the EU regulatory network

6.4.1. European Commission

None

6.4.2. The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

In view of reviewing the ENCePP's interaction and interface with EMA's Scientific Committees, ENCePP Steering Group asked the COMP representative to draft a reflection paper on "Optimisation of ENCePP impact on decision-making within the COMP". COMP members were asked to send any ideas/proposals they may have on the topic to the ENCePP COMP representative (Dinah Duarte) by 30 June 2016.

6.5. Cooperation with International Regulators

6.5.1. Food and Drug Administration (FDA)

The agenda from the EMA/FDA teleconference held on 24th May 2016 was tabled for information.

6.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

6.5.3. The Therapeutic Goods Administration (TGA), Australia

None

6.5.4. Health Canada

None

6.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

6.7. COMP work plan

6.7.1. Follow up on COMP Work Plan 2016

The Chair asked COMP members to start thinking of activities from the 2016 work plan that should be carried over to 2017 and of any new activities for 2017. A proposal for the 2017 COMP work plan will be circulated before the July meeting.

6.8. Planning and reporting

6.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2016 were circulated.

6.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

7. Any other business

7.1.1. EMA Business Pipeline activity and Horizon scanning

An overview of Centralised procedures starting Q2 2016 was circulated for information.

7.1.2. Dravet Syndrome Foundation Spain – Patient Data Platform

The EMA letter of support for Patient Data Platform for capturing patient-reported outcome measures for Dravet Syndrome was circulated for information.

7.1.3. Request for amendment of Orphan Designation

The COMP briefly discussed the request received from a sponsor in relation to the need of amending an existing orphan designation. The COMP was of the opinion that the therapeutic indication that the sponsor intends to pursue at marketing authorisation falls within the existing orphan designation and that an amendment is not needed. The COMP adopted the response to the sponsor.

[Post-meeting note: The response letter was tabled in MMD]

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 June 2016 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Judit Eggenhofer	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Guy Bouget	Expert - in person*	Lymphoma Coalition Europe	Revlimid appeal No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use
COMP: Committee for Orphan Medicinal Products
EC: European Commission
OD: Orphan Designation
PA: Protocol Assistance
PDCO: Paediatric Committee
PRAC: Pharmacovigilance and Risk Assessment Committee
SA: Scientific Advice
SAWP: Scientific Advice Working Party

Orphan Designation (*section 2 Applications for orphan medicinal product designation*)

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.
Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance (*section 3 Requests for protocol assistance with significant benefit question*)

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation (*section 4 Review of orphan designation for orphan medicinal products for marketing authorisation*).

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/